BPTF在肿瘤发生发展中的功能及相关分子机制研究

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摘要 染色质重塑过程通过影响染色质开放状态参与基因的转录调控. 作为染色质重塑复合物最大的亚基, 含溴域和锌指结构的蛋白BPTF可通过多种途径调控基因表达, 如参与染色质重塑过程, 影响DNA可及性; 作为独立的转录因子发挥作用; 与其他转录因子、组蛋白或长链非编码RNA等协同发挥作用, 并通过影响细胞增殖、迁移侵袭、干性维持、免疫应答等生物学过程参与肿瘤的发生发展, 发挥重要的促癌作用. 本文从BPTF的结构出发, 针对BPTF在肿瘤发生发展中的功能及相关分子机制、其自身的表达调控机制以及基于其结构与功能的小分子抑制剂的开发和应用现状等进行综述.

关键词 BPTF, 肿瘤, 转录调控

BPTF(bromodomain PHD-finger transcription factor)蛋白, 其基因位于17q24.3, 是染色质重塑复合物(nucleosome remodeling factor, NURF)最大的亚基^[1]. BPTF在人体各个组织广泛分布, 对于人体胚胎发育、免疫功能、干性维持等均有重要作用. 早期研究发现, BPTF缺失对早期原肠胚外胎盘锥体形成以及功能性远端内脏内胚层建立的影响, 可能与BPTF调控发育相关基因和信号通路有关^[2,3]; BPTF可通过与Smad2/TGF- β 相互作用, 募集NURF复合物在Wnt8a启动子区的聚集, 促进Wnt8a表达, 从而促进后部神经外胚层发育^[4]. BPTF还可以影响胸腺细胞发育^[5], 其缺失或突变, 可阻碍血清应答因子(serum response factor, SRF)

招募NURF, 继而抑制转录因子在BPTF依赖基因的结合, 引起胸腺细胞与发育相关基因亚群的异常表达, 导致CD4(+)CD8(int)T细胞发育停滞. 成熟T细胞稳态维持和调节性T细胞(regulatory T cells, Treg)的功能调控也离不开BPTF^[6]. BPTF可以正向调控Treg细胞中Foxp3的表达, 从而影响非淋巴器官中淋巴细胞浸润. 另一方面, BPTF与氧化应激传感器Keap1、自噬适配器P62/SQSTM1、泛素E3-连接酶Cullin-3等共同调控干扰素 γ (interferon γ , IFN- γ)诱导的主要组织相容性复合体(major histocompatibility complex, MHC) II类分子表达, 从而影响抗原呈递过程^[7]. 成体干细胞的自我更新和分化也部分依赖于染色质重塑改变染色质构型来

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完成^[8], 因此, BPTF在维持造血干细胞、乳腺干细胞、表皮干细胞等的干性特征中亦发挥至关重要的作用^[8-10].

癌症发生需要多种致癌基因驱动, 涉及多个信号通路共同发挥作用. 参与胚胎发育的基因突变或某些信号通路过度激活, 都可以影响癌症进程, 如Sox2, Hox, EMT转化和Wnt/ β -catenine信号通路等^[11-13]. 最初人们发现, 定位于17q24.3的BPTF基因易位表达有助于细胞获得癌症相关表型^[14]. 此后, BPTF在癌症发生发展中的作用逐步被揭示. 已有研究证明, BPTF在肺癌、肝癌、黑色素瘤、B细胞淋巴瘤、胰腺癌等多种癌症中发挥促癌作用, 通过多种途径促进癌细胞增殖、转移、干性维持, 影响抗肿瘤免疫等过程. 本课题组在BPTF的促癌功能以及相关分子机制研究方面做了大量的前期工作, 先后证明BPTF在肺癌细胞中可影响PI3K/AKT和MAPK信号通路, 促进肺癌细胞的生长与存活^[15], 并通过与核因子 κ B(nuclear factor kappa-B, NF- κ B)的p50亚基相互作用, 共同结合在环氧合酶2(cyclooxygenase-2, COX-2)的启动子区, 促进COX-2表达, 进而发挥促癌作用^[16]. 同时发现, BPTF在肝癌中通过转录调控人端粒酶逆转录酶(human telomerase reverse transcriptase, hTERT)的表达维持肝癌细胞干性, 促进肝癌细胞增殖与转移^[17].

1 BPTF发挥作用的结构基础

选择性剪接使BPTF存在三种不同亚型, 包括BPTF N-端结构, BPTF全长和BPTF融合蛋白^[18]. 1995年, Bowser等人^[19]通过可识别人类阿尔茨海默病相关神经元纤维病变的单克隆抗体Alz50对人类胎儿大脑cDNA文库进行了免疫筛选, 测序分析发现了一种名为胎儿阿尔茨海默病抗原(fetal Alz-50-reactive clone 1, FAC1)的新基因. 1996年, Zhu和Bowser^[20]鉴定分析发现, *FAC1*基因编码含810个氨基酸的蛋白质, FAC1蛋白包含一个锌指结构, 核定位序列及一段可能在蛋

白互作中起作用的酸性结构域. 它不仅可以在核内序列特异性结合DNA片段, 并发挥转录因子的作用^[21], 还可以通过与核蛋白Myc相关锌指蛋白ZF87/MAZ相互作用, 共同调控基因表达^[22]. FAC1可能是BPTF较短的一种转录本, 只包含BPTF的N-端结构域^[2]. 2000年, Jones等人^[23]通过在EST数据库中搜索新的溴域相关基因, 发现并鉴定了BPTF蛋白的完整序列. BPTF蛋白由2781个氨基酸组成, 具有转录调节子的典型特征, 包括C端的溴结构域、锌指结构、富含谷氨酰胺的酸性结构域和N端的锌指结构, DDT DNA结合结构域^[24](图1). 现有研究证明, BPTF既可通过C端溴域和近溴域的锌指结构, 分别特异性识别并结合16位乙酰化赖氨酸(histone H4 lysine 16 acetylation, H4K16ac)和组蛋白4位甲基化赖氨酸(histone H3 lysine 4 trimethylation, H3K4me2/3)^[25-27], 也可通过DNA结合结构域, 直接结合在下游靶基因启动子区, 发挥转录调控作用, 影响相关蛋白表达, 还可以作为转录辅因子, 与其他因子共同发挥调控作用. BPTF还会与其他基因融合, 形成融合蛋白, 参与疾病的进程. 例如, 癌基因融合是婴幼儿白血病的一个重要驱动因素^[28], 2018年Roussy等人^[29]在急性巨核细胞白血病(acute megakaryoblastic leukemia, AMKL)中鉴定了两种新型NUP98-BPTF融合蛋白亚型, 这两种亚型属于剪接变体, 均由BPTF的C端与NUP98蛋白N端部分融合形成蛋白框架. 这种融合蛋白的发现, 可能为AMKL的鉴定提供新的标志物.

2 BPTF在肿瘤发生发展中的功能

2.1 BPTF对肿瘤细胞增殖的影响

染色体17q部分增益是出现在各种不同癌症中的一种常见的异常现象, 许多位于17q的基因在恶性肿瘤特别是在胶质瘤、肺癌等的发生发展中发挥关键促癌作用^[30,31]. Bugarim等人^[14]发现, 发生在染色体17q24.3位点的基因断点, 定位于BPTF基因, 可导致内源性BPTF表达上调, 增强人肺胚胎来源细胞的体外增殖与

图1 BPTF结构示意图

Figure 1 Structural diagram of BPTF protein

集落形成能力,使得细胞具备促癌表型.研究还发现,在肺癌及黑色素瘤细胞系中敲低BPTF,可以抑制细胞增殖,诱导细胞凋亡,使细胞周期进程阻滞在G₀/G₁期^[15,32].在肝癌和卵巢癌中下调BPTF的表达,能有效抑制癌细胞的增殖能力^[17,33].胶质瘤临床样本分析则显示,BPTF过度表达与胶质瘤异常增殖相关^[34,35].

2.2 BPTF对肿瘤细胞转移的影响

癌细胞从原发肿瘤上脱离,侵入血液或淋巴组织,并经血液或淋巴系统扩散,渗入转移部位,生长形成继发性肿瘤的过程称为癌症转移^[36].上皮-间充质转化(epithelial-mesenchymal transition, EMT)是癌细胞转移过程中的重要一步.已分化的上皮细胞具有活动性弱、极化的特点,与之相对的,间充质细胞则具备活动性强、非极化的特点.在癌症转移发生初期,已分化的上皮细胞通过细胞间连接嵌入细胞群后,溶解其胞间连接,并转化为间充质细胞,从而增强其迁移及侵袭能力^[37,38].Xiao等人^[39,40]先后分析了结肠癌及肝癌病人正常组织与癌组织BPTF与EMT相关蛋白标志物表达的相关性,结果显示,BPTF在肝癌与结肠癌中均与促进EMT进程相关蛋白协同表达,表明BPTF可能通过参与EMT进程促进肝癌及结肠癌转移.Zhao等人^[17]进一步在肝癌细胞及肝癌肺转移模型中证明了BPTF对肝癌转移的促进作用;Dar等人^[32]的研究表明,BPTF促进黑色素瘤细胞肺转移;Pan等人^[34]发现,BPTF过表达可增强胶质瘤细胞的迁移侵袭能力;而Koedoot等人^[41]则确定BPTF是三阴性乳腺癌细胞的转移驱动基因.

2.3 BPTF对肿瘤细胞干性维持的影响

肿瘤干细胞(cancer stem cells, CSCs),是指具有自我更新能力与分化潜能的一小部分癌细胞群体.肿瘤复发、转移和耐药性的产生均与CSCs紧密相关,靶向CSCs已成为肿瘤治疗的重要策略^[42,43].研究表明,BPTF对于胚胎发育和正常干细胞的干性维持至关重要.又因为EMT转化与肿瘤细胞的干性获得紧密相关,而BPTF可影响肿瘤细胞EMT转化过程^[44],因此,对BPTF是否能影响CSCs干性的研究和报道越来越多.在肝癌细胞中,敲低BPTF可降低肝癌细胞体外成球能力,并减少干性相关蛋白CD44, CD133等的表达^[17];在c-Myc驱动的侵袭性B细胞淋巴瘤中,BPTF对于正常B

细胞的分化至关重要^[45];成人和儿童高级别胶质瘤中,BPTF在肿瘤细胞维持自我更新能力的过程中必不可少,BPTF缺失导致具有胶质特征的肿瘤细胞呈现出分化神经元的特征^[35].

2.4 BPTF对抗肿瘤免疫的影响

免疫系统的稳态维持是保证人体机能正常的重要环节,而肿瘤因其特殊的免疫微环境可逃过免疫系统的监视和杀伤作用,重启抗肿瘤免疫效应是目前公认的扼制肿瘤进程的最有希望的治疗策略^[46].BPTF参与肿瘤的免疫逃逸,既可影响肿瘤微环境固有的免疫反应,又可影响T细胞介导的细胞免疫过程.BPTF可抑制天然细胞毒性受体(natural cytotoxic receptor, NCR)介导的自然杀伤细胞(natural killer cells, NK cells)的抗肿瘤活性^[47],影响NK细胞的杀伤能力,又可通过多种途径阻碍T细胞成熟.一方面,BPTF可影响IFN- γ 诱导的单核巨噬细胞、B细胞、树突状细胞等抗原呈递细胞表面MHC II类分子表达而抑制抗原呈递过程,进而影响T细胞成熟^[7];另一方面,BPTF通过NURF复合物下调免疫蛋白酶体亚单位Psmb8和Psmb9以及抗原转运体基因*Tap1*和*Tap2*表达,通过影响抗原肽的产生而影响由MHC I类分子介导的抗原呈递过程,影响T细胞成熟.因此,当BPTF缺失或低表达的肿瘤细胞与CD8⁺ T细胞共培养时,会导致CD8⁺ T细胞对肿瘤细胞的杀伤力增强^[48].

3 BPTF影响肿瘤进程的相关分子机制

3.1 BPTF通过染色质重塑过程,影响DNA可及性

染色质重塑复合物由四个亚单位组成,包括ISWI ATP酶、最大亚基NURF301、WD重复蛋白NURF55、无机焦磷酸酶NURF38^[49].NURF可催化核小体以ATP依赖的方式滑动,从而引起核小体在启动子区的重新定位,使染色质呈开放状态,允许转录因子、转录辅因子以及RNA聚合酶II在启动子区的募集,介导基因表达^[50-52].BPTF(NURF301)作为NURF复合物最大亚基,可通过由NURF介导的染色质重塑过程,影响DNA可及性.全基因组测序结果表明,BPTF可维持染色质中增强子的开放状态,从而实现对乳腺干细胞(mammary stem cells, MaSCs)自我更新能力的调节;对成人造血干细胞(hematopoietic stem cells,

HSCs)的干性调节主要原因也在于其能通过影响染色质可及性,激活干性相关基因表达^[9,10]。BPTF敲低则会引起染色质可及性发生变化,导致c-Myc在DNA上的募集减少,阻碍c-Myc对下游靶基因的转录调控作用^[53]。

3.2 BPTF作为转录因子发挥作用

人端粒酶逆转录酶的异常活化是维持癌细胞无限增殖的关键要素^[54]。hTERT可通过多种信号通路参与肿瘤细胞的增殖、迁移侵袭、干性及化疗、放疗耐药性的产生和维持,并在肿瘤复发与转移中发挥重要作用^[55,56]。本课题组^[17]的前期研究表明,BPTF可以不依赖于H3K4me3的方式结合在hTERT启动子区(-902~-321),调控hTERT转录和表达,进而影响肝癌细胞的增殖、迁移侵袭和干性,并最终影响体内的成瘤能力和肺转移等。

NCR是NK细胞表面的一类激活型受体^[57],可通过与细胞表面硫酸乙酰肝素蛋白聚糖(heparan sulfate proteoglycan, HSPG)的硫酸乙酰肝素链(heparan sulfate, HS)结合,活化NK细胞,使其具有溶解细胞活性^[58]。研究表明,BPTF可结合在乙酰肝素酶(heparanase, Hpse)启动子区调节元件上,调控其转录活性,使Hpse表达上调,而Hpse表达升高可降低细胞表面HSPG丰度,进而影响NK细胞活化和其功能^[47]。

COX-2在肺癌中高表达,并与肺癌血管生成、转移、抗凋亡、抗肿瘤免疫相关^[59,60]。本课题组^[16]前期研究利用生物素-链霉素和素垂钓实验结合质谱分析发现,BPTF在COX-2启动子区有结合,进一步分析确定了NF- κ B的p50亚基协同转录调控COX-2表达,进而影响肺癌细胞的增殖与体内成瘤性,提示BPTF/p50/COX-2轴可能为肺癌治疗的潜在靶标。

3.3 BPTF通过与其他蛋白分子互作发挥作用

(1) BPTF促进c-Myc蛋白表达并作为转录辅因子协同c-Myc调控下游靶基因表达。c-Myc在几乎所有人类肿瘤中均过度表达。作为明星致癌转录因子,其可与Max蛋白形成异源二聚体,序列特异性结合在靶标基因的启动子区影响下游靶基因的转录,进而影响癌细胞增殖、周期进程、凋亡、分化、代谢和血管生成等重要生理功能^[61-63]。早期研究发现,在胶质瘤中,BPTF可能通过影响Myc通路发挥促癌作用^[34]。Zhan等人^[64]

研究表明,环状RNA circCTIC1募集NURF复合物在c-Myc启动子区,通过依赖于BPTF的转录调控c-Myc表达,进而影响结肠癌的自我更新能力。

BPTF不仅可以调控c-Myc自身表达,同时也是c-Myc发挥转录调控作用必不可少的辅因子。c-Myc可与BPTF相互作用协同调控下游靶基因的转录,BPTF表达量与c-Myc驱动的转录信号呈正相关^[53,65]。敲低BPTF可导致c-Myc在DNA上的募集减少,进而影响c-Myc调控的靶基因表达。基于此,Richart等人^[45]研究发现,BPTF在c-Myc驱动的B细胞淋巴瘤中发挥关键作用,BPTF缺失或表达减少可有效减缓c-Myc驱动的B细胞淋巴瘤进程。

(2) H2A.Z募集BPTF/WDR5发挥转录调控作用。H2A.Z是组蛋白H2A的一种变体,可优先渗入转录起始位点(transcription start site, TSS)附近的核小体内,能通过改变染色体结构和募集相关转录因子调控下游靶基因表达^[66-68]。H2A.Z在膀胱癌中可激活周期相关蛋白表达,促进肿瘤细胞的周期进程。ChIP-seq结果显示,这可能与它能募集BPTF和WDR5至周期相关蛋白启动子区共同调控转录有关^[69]。Perell等人^[70]的进一步研究则表明,H2A.Z二乙酰化的4位和11位赖氨酸残基与BPTF蛋白的溴域具有高亲和力,可以直接相互作用。

(3) LncRNA NMR通过募集BPTF发挥促癌作用。长链非编码RNA(long noncoding RNAs, lncRNAs)是各种生物过程的关键调节因子,其突变和失调在癌症过程中发挥关键作用,它可以通过包括与蛋白质互作等在内的多种途径调控基因表达,进而影响癌症进程^[71,72]。Li等人^[73]证明了LncRNA NMR在食管鳞状细胞癌(esophageal squamous cell carcinoma, ESCC)中的促癌作用,NMR是ESCC转移和耐药的关键调节因子,可以募集BPTF到染色质特定区域,活化ERK1/2表达,进一步促进转移相关蛋白MMP3和MMP10的表达,进而促进ECSS转移。

3.4 BPTF自身表达调控机制

(1) MITF调控BPTF表达。小眼畸形相关转录因子MITF可影响黑色素细胞分化,促进黑色素瘤进展。Dar等人^[74]的研究表明,MITF在黑色素瘤中靶向BPTF促进肿瘤细胞存活。BPTF启动子区存在MITF结合序列,染色质免疫共沉淀(chromatin immunoprecipitation, ChIP)和荧光素酶活性实验证明了MITF在BPTF启动

子区的结合以及MITF对于BPTF的转录调控. 敲低MITF可导致BPTF及BCL2表达下调, 黑色素瘤细胞增殖受阻, 而BPTF过表达则可部分逆转MITF敲低产生的增殖抑制. 同时, BPTF还可以作为MITF转录调控的辅因子, 协同其调控基因表达^[75,76].

(2) METTL14调控BPTF表达. RNA甲基转移酶样蛋白METTL14可通过下调BPTF发挥抑癌作用, 是判断透明肾细胞癌预后的标志物之一^[77]. METTL14介导的m⁶A修饰降低了BPTF mRNA稳定性, 导致BPTF表达下调, 进而影响细胞内表观遗传调控和代谢重塑. METTL14缺陷则会引起细胞内BPTF的累积, 构成激活下游靶标的超级增强子, 导致糖酵解重编程^[78].

(3) MicroRNA调控BPTF表达. MicroRNA自被发现以来, 迅速成为相关基础研究领域的热点, 其在发育与肿瘤进程中的关键作用屡被报道. 进一步了解microRNA发挥作用的机制对于丰富和扩大人们对于microRNA的认知, 实现其临床转化意义重大^[79]. Pan等人^[80]研究发现microRNA-3666在肺癌中直接靶向BPTF 3'-UTR, 负向调控BPTF的表达, 抑制PI3K/AKT通路和EMT转化, 进而抑制肺癌细胞的增殖与转移. Gan等人^[81]的研究则表明, miR-1269可能通过靶向BPTF在肝癌中发挥促癌作用.

3.5 Circ-BPTF发挥作用的分子机制

CircRNA是真核生物中共价闭合的内源性生物分子, 没有5'-3'极性, 也不含polyA尾, 其表达受顺式作用元件和反式作用因子调控, 具有组织和细胞特异性^[82,83], 通过结合microRNA、转录因子、RNA结合蛋白等发挥生物学功能. 最新研究显示, circRNA还能通过与宿主基因特定位点结合, 影响宿主基因的表达^[84,85]. BPTF外显子21~27通过反向剪接获得的circRNA, circ-BPTF(hsa_circ_0000799)在膀胱癌细胞和组织中高表达, 促进膀胱癌进程. 进一步分子机制研究表明, circ-BPTF可吸附miR-31-5p, 减弱miR-31-5p对RAB27A表达的抑制, 促进RAB27A表达, 并最终发挥促癌作用^[86].

4 BPTF小分子抑制剂的开发与应用研究

溴域是含约110个氨基酸的蛋白模块, 可以识别包括组蛋白在内的乙酰化赖氨酸位点. 含溴域蛋白的表

达失调与癌症等多种疾病相关, 针对溴域开发小分子抑制剂提供了一种新的治疗策略^[87-90]. 现阶段, 溴域抑制剂的开发主要针对BET家族蛋白, 并已进入临床试验阶段. 近些年, 含溴域的非BET家族蛋白BPTF因其强大的促癌功能逐渐被重视, 以BPTF溴域为靶点的抑制剂研究和开发工作也逐渐展开^[87,91].

AU1是第一个被合成的选择性作用于BPTF溴域的抑制剂, 在透明肾细胞癌体外细胞及体内荷瘤实验中被证明发挥抑癌作用^[78,89]. 在三阴性乳腺癌中, AU1也被证明可提高表柔比星对癌细胞的杀伤作用, 增加癌细胞中拓扑异构酶二和DNA之间的交联, 促进DNA损伤以及相关的自噬^[92]. 除AU1以外, 其他靶向BPTF溴域的抑制剂, 如C620-0696, cpd8和cpd10, 均被报道可降低BPTF下游靶基因c-Myc的表达, 但是这些抑制剂能否在BPTF和c-Myc对下游靶基因的协同表达调控中发挥作用仍需要进一步研究和阐释^[93,94]. 另一种已被报道的BPTF溴域抑制剂NVS-BPTF-1, 经研究发现不能引起抗原呈递相关蛋白psmb8, psmb9, Tap1和Tap2表达的变化^[93,95], 表明BPTF抑制剂用于c-Myc驱动的肿瘤治疗及抗肿瘤免疫治疗方面还有很大的未知空间值得去探索和研究, 从而为BPTF抑制剂的临床转化和应用提供足够的理论和实验依据.

5 总结与展望

癌症发生是一个错综复杂的病理过程, 涉及到多基因、多通路共同发挥作用. BPTF已被证明在多种癌症中异常表达并发挥促癌作用, 参与癌细胞增殖、迁移侵袭、干性维持和抗肿瘤免疫等生物学功能(表1), 可作为包括肺癌、肝癌、结肠癌、黑色素瘤、胶质瘤、透明肾细胞癌和卵巢癌等在内的多种肿瘤的独立预后标志物或潜在治疗靶点. BPTF通过多种机制发挥促癌作用, 如可作为NURF复合亚基影响染色质重塑过程, 通过表观遗传途径调控DNA可及性; 可作为转录因子或转录辅因子直接或间接结合在靶基因启动子区发挥转录调控作用(图2); 可作为下游靶基因被非编码RNA或参与肿瘤进程的关键蛋白所调控促进肿瘤发生发展. 特别值得指出的是, BPTF已被证明可影响细胞增殖相关通路及凋亡、周期相关蛋白的表达; 可影响EMT转化和染色质开放状态促进癌症转移与干性维持; 可影响机体固有免疫与细胞免疫过程, 包括

表 1 BPTF在肿瘤中的功能及可能的相关分子机制

Table 1 Functions and related molecular mechanisms of BPTF in different cancers

肿瘤类型	功能作用	可能的相关分子机制
黑色素瘤	促进增殖, 维持干性	MITF/BPTF
肺癌	促进增殖(促进周期, 抑制凋亡)、迁移侵袭	BPTF/p53/COX-2, miR-3666/BPTF
肝癌	促进增殖、迁移侵袭、维持干性	BPTF/hTERT
神经胶质瘤	促进增殖、迁移侵袭、维持细胞自我更新能力	影响Myc通路
膀胱癌	促进增殖(促进周期)	H2A.Z/BPTF/WDR5
结肠癌	促进肿瘤干细胞自我更新能力	CircCTIC1/BPTF/c-Myc
卵巢癌	促进增殖(诱导凋亡)、迁移侵袭	影响EMT及凋亡通路
透明肾细胞癌	促进糖酵解重编程, 远端肺转移	METTL14/BPTF
食管鳞状细胞癌	促进转移	NMR/BPTF
侵袭性B细胞淋巴瘤	促进c-Myc驱动肿瘤进程	BPTF/c-Myc
乳腺癌	抑制肿瘤微环境中自然杀伤细胞抗肿瘤活性	BPTF/Hpse

图 2 BPTF调控基因表达的不同作用模式. A: BPTF所在的NURF复合物影响染色质重塑, 使染色质呈开放状态, 有利于转录调控因子的结合, 启动基因转录; B: BPTF本身作为转录因子调控基因表达. a: BPTF直接结合在基因启动子区, 激活转录; b: BPTF与其他转录因子相互作用, 协同调控基因转录

Figure 2 Different modes of BPTF in regulating expressions of target genes. A. The NURF complex that BPTF resides in affects chromatin remodeling and leaves chromatin loose, which facilitates the binding of transcription regulatory factors and initiates gene transcription; B. BPTF acts as a transcription factor to regulate gene expression. a: BPTF binds directly to the gene promoter and activates gene transcription; b: BPTF synergizes with other transcription factors to regulate gene transcription

影响Hpse表达, 影响NCR介导的NK细胞溶解能力, 影响psmb8, psmb9, Tap1和Tap2表达进而影响抗原呈递, 影响T细胞成熟. 并且, BPTF可以调控关键致癌因子c-Myc表达, 同时又能做为转录辅因子介导c-Myc对下游靶基因的调控, 抑制BPTF与c-Myc相互作用, 可能成为c-Myc驱动的肿瘤的一种潜在治疗策略.

基于BPTF在多种肿瘤中发挥强大的促癌功能, BPTF抑制剂极有可能成为肿瘤治疗的新策略和新希望. 以溴域为靶点的BPTF抑制剂的研究和开发目前正开展得如火如荼, 但BPTF促癌功能的发挥是否完全或部分依赖于此功能域仍有待探索. 对于BPTF抑制剂的

研发尚处于初级阶段, 寻找特异性更强、毒副作用更小的化合物势在必行. BPTF锌指结构与组蛋白H3K4me2/3的直接结合以及这种结合在BPTF功能发挥中的重要作用使得针对此类结构域的抑制剂的开发变得格外有意义, 但目前仍是一个挑战. 此外, BPTF促癌功能发挥的分子途径和作用机制仍然有待进一步挖掘和阐释. 相信随着对其作用机制理解的进一步拓展和延伸, 可以更有效地开发BPTF抑制剂并将其用于抗肿瘤治疗研究. 总之, BPTF有望成为肿瘤治疗的极具潜力的候选靶标, 实现其临床转化意义重大但依然任重道远.

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Functions and related molecular mechanisms of BPTF in tumorigenesis and development

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Chromatin remodeling is involved in gene transcriptional regulation as it affects the chromatin opening status. As the largest subunit of chromatin remodeling complex, bromodomain PHD-finger transcription factor (BPTF) containing bromine domain and zinc finger structure can regulate gene expression through various ways, such as participating in chromatin remodeling and affecting DNA accessibility; acting as independent transcription factors; synergistically acting with other transcriptional factors, histone or long-chain noncoding RNAs, and is involved in tumorigenesis and development to promote cancer progression by influencing cellular proliferation, migration and invasion, stemness maintenance, immune response, and other biological processes. This paper reviews the structure of BPTF, the function and related molecular mechanism of BPTF in tumor development and its expression regulation mechanism, as well as the development and application status of small-molecule inhibitors based on their structure and function.

BPTF, tumor, transcriptional regulation

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